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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,749	12/22/2004	Takashi Nakayama	1422-0651PUS1	3018

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BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

EXAMINER	
SGAGIAS, MAGDALENE K	
ART UNIT	**PAPER NUMBER**
1632	

NOTIFICATION DATE	DELIVERY MODE
07/24/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/518,749	NAKAYAMA ET AL.	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 5/14/07.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-19 is/are pending in the application.

4a) Of the above claim(s) 4-9,15,16,18 and 19 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-3,10-14 and 17 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 22 December 2004 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 12/11/06;3/22/05;12/22/04.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-19 are pending. Claims 1-18 are under consideration.

Applicant's election with traverse of group I in the reply filed on 5/14/07 is acknowledged. The traversal is on the ground(s) the Examiner offers Arnold et al, as evidence that the present invention does not make a "contribution" over the prior art. This is not found persuasive because Applicant has not provided any arguments, reasoning or evidence that Arnold is not appropriate in establishing the knowledge of a method for producing a substantially isolated neural cell by cultivating mouse ESCs in suspension in the presence of an astrocyte-conditioned medium. Applicants have not provided arguments that the method of producing substantially isolated cells neural cells of group I by using the method of Arnold is not a relevant argument against lack of unity. The guidelines in the MPEP are clear national stage applications follow PCT lack of unity guidelines. These guidelines state one means in which to show the invention lacks a special technical feature is to provide a prior art reference demonstrating the invention or some part of the invention was known in the art at the time of filing. The reference of Arnold et al, does this. Groups I and II are rejoined, thus claims 1-18 are under consideration.

The requirement is still deemed proper and is therefore made FINAL.

Claim **19** is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 5/14/07.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims **1-8, 10-18** are rejected under 35 U.S.C. 102(b) as being anticipated by **Weiss et al,** (US 5,981,165).

Weiss et al, teaches a method for producing an isolated neural cell, by culturing a suspension of embryonic stem cells in the presence of ingredients substantially equivalent to an astrocyte conditioned medium, (column 12, example 3) **(claims, 1, 10-11, 13, 16-18)**. Further Weiss teaches the formation of neurospheres (figure 2) (**claims 4-8**).

Weiss teaches the embryonic stem cells are murine (**claims, 2-3**).

Weiss teaches a method of producing a neuron by carrying a suspension of embryonic stem cells in the presence of ingredients substantially equivalent to an astrocyte conditioned medium in the state of adhesion of the neural stem cells to an adhesive culture substratum by plating the cells onto poly-L-ornithine coated glass cover slips, in the complete medium with rat B49 glial cell line-derived conditioned medium in the absence of bFGF, in the presence of FGF2 and in the presence of ingredients substantially equivalent to astrocyte conditioned medium (example 8) (**claim, 10**).

Weiss teaches the substantially isolated neuron expresses tyrosine hydroxylase (example 2) (**claim 14**).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims **1-3, 10-12** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Zhang et al,** (Nature Biotechnology, 19: 1129-1133, 2001, IDS) in view of **Flax et al,** (Nature, 16: 1033-1039, 1998).

Zhang teaches human embryonic stem (ES) cell-derived neural precursors generate all three CNS cell types in vitro and the isolated neural precursors expanded as free-floating cell aggregates in a suspension similar to "neurosphere" cultures (p 1129, 2nd column last paragraph). Zhang teaches the in vitro differentiation of the ES cell-derived neural precursors was induced by withdrawn of FGF-2 and plating on the state of adhesion of the neural stem cell precursor by plating on ornithine and laminin substrate (p 1130, 1st column, 2nd paragraph). After 7-10 days after plating differentiated neurons expressed neuronal markers MAP2ab, β_{III}-tubulin, GABA, tyrosine hydroxylase (TH), GFAP (p 1130, 2nd column, 1st paragraph). Zhang teaches the suspension of human ES in ingredients substantially equivalent to an astrocyte conditioned medium and the absence of EGF (p 1132-1133 and figure 3). Zhang teaches on a pragmatic level, the in vitro generation of neural tube-like structures and the possibility of isolating these structures on the basis of their differential adhesion provides a simple yet efficient approach for generating human ES-derived neural precursors in high purity (p 1131, 2nd column, 3rd paragraph). Zhang suggests because undifferentiated ES cells and precursors to other lineages may form tumors and foreign tissues, the generation of purified somatic

populations of cells is a key prerequisite for the development of ES cell-based neural transplant strategies (p 1131, 2nd column, 3rd paragraph). Zhang teaches the chemically defined culture system they described provides an opportunity to explore the effects of single factors on human neuroepithelial proliferation and specification in vitro (p 1131, 2nd column, last paragraph). Zhang differs from the claimed invention by not teaching the cryopreservation of neural stem cells.

However, at the time the claimed invention was made, **Flax** et al, teach functional cryopreservable human neural stem cells can be propagated in culture in vitro (p 1037-1038). As such, Flax et al provide sufficient motivation for one of ordinary skill in the art to apply the cryopreservation methodology of Flax to the neural stem cell methodology of Zhang to explore the effects of single factors on human neuroepithelial proliferation and specification in vitro.

Accordingly, in view of the teachings of Flax et al, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the neural stem cell methodology of Zhang by cryopreserving the produced neurons with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification as Zhang has suggested the generation of purified somatic populations of cells is a key prerequisite for the development of ES cell-based neural transplant strategies. Thus, the claimed invention as a whole, is clearly prima facie obvious in the absence of evidence to the contrary.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-18 are rejected under 35 U.S.C. 102(b) as anticipated by **Zhang et al,** (Nature Biotechnology, 19: 1129-1133, 2001, IDS) or, in the alternative, under 35 U.S.C. 103(a) as obvious over **Pataky et al,** (Exp Neurol, 163(2): 357-372, 2000 (IDS)).

Zhang teaches human embryonic stem (ES) cell-derived neural precursors generate all three CNS cell types in vitro and the isolated neural precursors expanded as free-floating cell aggregates in a suspension similar to "neurosphere" cultures (p 1129, 2nd column last paragraph). Zhang teaches the in vitro differentiation of the ES cell-derived neural precursors was induced by withdrawn of FGF-2 and plating on the state of adhesion of the neural stem cell precursor by plating on ornithine and laminin substrate (p 1130, 1st column, 2nd paragraph). After 7-10 days after plating differentiated neurons expressed neuronal markers MAP2ab, β_{III}-tubulin, GABA, tyrosine hydroxylase (TH), GFAP (p 1130, 2nd column, 1st paragraph). Zhang teaches the suspension of human ES in ingredients substantially equivalent to an astrocyte conditioned medium and the absence of EGF (p 1132-1133 and figure 3). Zhang teaches on a pragmatic level, the in vitro generation of neural tube-like structures and the possibility of isolating these structures on the basis of their differential adhesion provides a simple yet efficient approach for generating human ES-derived neural precursors in high purity (p 1131, 2nd column, 3rd paragraph). Zhang suggests because undifferentiated ES cells and precursors to other lineages may form tumors and foreign tissues, the generation of purified somatic populations of cells is a key prerequisite for the development of ES cell-based neural transplant strategies (p 1131, 2nd column, 3rd paragraph). Zhang teaches the chemically defined culture system they described provides an opportunity to explore the effects of single factors on human neuroepithelial proliferation and specification in vitro (p 1131, 2nd column, last paragraph).

Zhang differs from the claimed invention by not teaching the culturing of stem cell spheres in the presence and then in the absence of bFGF and/or EGF for obtaining glial cell as a cell migrating from the stem cell sphere.

However, at the time the claimed invention was made, Pataky teaches that fibroblast growth factor produced differential effects on survival and neurite outgrowth from identical bulbospinal neurons in vitro. Pataky teaches that astrocytes synthesize a variety of trophic factors and astrocyte conditioned medium also promoted the survival of bulbospinal neurons (abstract).

Accordingly, in view of the teachings of Pataky et al, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the neural stem cell methodology of Zhang by progressive steps of adding bFGF or EGF to obtain neural stem cells and then culture the stem cells in the presence of bFGF or EGF to obtain glial cells with a reasonable expectation of success because Pataky states that astrocytes produce neural nutritional factors such as FGF2. One of ordinary skill in the art would have been sufficiently motivated to make such a modification as Zhang has suggested the generation of purified somatic populations of cells is a key prerequisite for the development of ES cell-based neural transplant strategies. Thus, the claimed invention as a whole, is clearly prima facie obvious in the absence of evidence to the contrary.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims **1, 4, 7-8, 10, 11, 13-18** are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "substantially" in claim **1, 4, 7-8, 10, 11, 13-18** is a relative term which renders the claim indefinite. The term "substantially" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear what are the limits of the culture ingredients that are equivalent to the conditioned medium.

Claim **1** recites the limitation "the suspension" in 2nd line. There is insufficient antecedent basis for this limitation in the claim.

Claim **10** recites the limitation "the state" in 3rd line. There is insufficient antecedent basis for this limitation in the claim.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Magdalene K. Sgagias, Ph.D.
Art Unit 1632

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP 1600/1630